

# Enzyme Therapy for Non-Alcoholic Steatohepatitis (NASH) and Related Disorders

## TECHNICAL FIELD

Therapeutic: NASH and related disorders (2005-0504)

## BACKGROUND

NASH is a disease of the liver characterized by inflammation, damage to hepatocytes, and compromise of liver function that may progress to an irreversible stage. Typically, NASH and other related Nonalcoholic Fatty Liver Diseases (NFLD) involve hepatic inflammation with fat accumulation and mimic alcoholic hepatitis in patients who seldom or never consume alcohol. Additionally, NASH involves the development of histologic changes in the liver comparable to those induced by excessive alcohol intake including macrovesicular and/or microvesicular steatosis, lobular and portal inflammation, occasionally with fibrosis and cirrhosis. NASH is commonly associated with hyperlipidemia, obesity, and type II diabetes mellitus and has been frequently associated with excessive fasting, jejunioleal bypass, total parental nutrition, chronic hepatitis C, Wilson's disease, and adverse drug effects from corticosteroids, calcium channel blockers and high dose synthetic estrogens.

Currently there is no established therapy for NASH. Weight loss is commonly prescribed since NASH is often found in obese patients. NASH develops in at least 10-20% of obese adolescents and adults and in 5-10% of those that are overweight. It is estimated that there are over 500,000 people in the U.S. with NASH or some form of NFLD. Current market estimates to treat this disorder are approximately \$500 million per year.



## TECHNOLOGY

Lysosomal acid lipase (LAL) is a possible candidate for the treatment and/or prevention of NASH and related disorders. In laboratory studies, LDLR(-/-) mice fed a high fat, high cholesterol diet developed fatty liver transformations, including micro- and macrovesicular fatty changes and inflammatory cell infiltration resembling NFLD. Intravenous administration of exogenous LAL led to significant reductions of inflammation and microvesicular fat and a disappearance of macrovesicular fat deposits in the livers of these animals. Control mice receiving LAL showed no adverse effects. An effective dose of human LAL can be administered on a regular basis by the usual exogenous routes or by endogenous routes from vectors expressing LAL in hepatocytes or hematopoietic or other stem cells in a continuous or controlled manner. The LAL technology represents an opportunity to develop a treatment for a common disorder where no current therapy exists and for a disease that accompanies many other common disorders in children and adults such as obesity, diabetes, and hepatitis C. Outcomes can easily be assessed with serum or tissue biomarkers, biopsies or other convenient markers. The treatment allows the affected hepatocytes to return to some degree of normal activity, providing patients with the return of several physiologic functions compromised by NASH.

## APPLICATIONS

1. Therapeutic to treat and/or prevent NASH and related diseases
2. Research tool

## ADVANTAGES

- Potential to develop new therapeutic market

## INVESTIGATOR

Gregory Grabowski, MD  
Professor and Division Head  
Division of Human Genetics  
Cincinnati Children's Hospital Medical Center

## STATUS

Patent applications pending.

## CONTACT

Luna Mukherjee, PhD  
Technology Manager  
[Luna.Mukherjee@cchmc.org](mailto:Luna.Mukherjee@cchmc.org)  
513-803-0308

# Enzyme Therapy for Non-Alcoholic Steatohepatitis (NASH) and Related Disorders

## THE INVENTOR

Gregory A. Grabowski, MD  
Professor and Division Head, Human Genetics  
Professor of Pediatrics and Molecular Genetics, Biochemistry and Microbiology

## BACKGROUND

**MD:** University of Minnesota Medical School, Minneapolis, MN, 1970 to 1974.

**Residency:** Department of Pediatrics, University of Minnesota, Minneapolis, MN, 1974 to 1976.

**Fellowship:** Medical Genetics, Department of Pediatrics and the Dight Institute for Human Genetics, University of Minnesota, Minneapolis, MN, 1976 to 1979.

**Certification:** American Board of Pediatrics, 1980; American Board of Medical Genetics; Clinical Genetics, 1987; Clinical Biochemical Genetics, 1987; Clinical Molecular Genetics, 1993.



Dr. Grabowski investigates the pathogenesis of selected lysosomal storage diseases. Studies range from gene transfer, purification and characterization of recombinantly produced selectively mutated enzymes, knock-in and knock-out mouse generation, and genome wide studies of transcriptomes and proteomes. These studies use high-density microarrays and bioinformatics to identify molecular signatures of lysosome-based biological processes, and integrative morphology to define the cellular basis of molecular signatures and the phenotype of organs of the digestive system in gene-targeted mice.

The overall goal of his research program is to define the nature of the signature pathways in disease pathogenesis, and the evolution of the disease phenotypes in mouse models that have been developed as prototypes for selected human diseases. By combining biochemistry/molecular genetics, high-throughput functional genomics, and histopathologic approaches, new strategies will be developed for effective therapeutic interventions and their evaluation by novel biomarkers. Particular emphasis relates to the regulatory role of macrophages or the tissue-specific injury of the liver, spleen and intestine, and the molecular signals controlling the process.